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Background—The purpose of this study was to examine the prevalence of abnormalities in cardiac structure and function present in patients with heart failure and a preserved ejection fraction (HFPEF) and to determine whether these alterations in structure and function were associated with cardiovascular morbidity and mortality.

Methods and Results—The Irbesartan in HFPEF trial (I-PRESERVE) enrolled 4128 patients; echocardiographic determination of left ventricular (LV) volume, mass, left atrial (LA) size, systolic function, and diastolic function were made at baseline in 745 patients. The primary end point was death or protocol-specific cardiovascular hospitalization. A secondary end point was the composite of heart failure death or heart failure hospitalization. Associations between baseline structure and function and patient outcomes were examined using univariate and multivariable Cox proportional hazard analyses. In this substudy, LV hypertrophy or concentric remodeling was present in 59%, LA enlargement was present in 66%, and diastolic dysfunction was present in 69% of the patients. Multivariable analyses controlling for 7 clinical variables (including log N-terminal pro-B–type natriuretic peptide) indicated that increased LV mass, mass/volume ratio, and LA size were independently associated with an increased risk of both primary and heart failure events (all $P<0.05$).

Conclusions—Left ventricular hypertrophy or concentric remodeling, LA enlargement, and diastolic dysfunction were present in the majority of patients with HFPEF. Left ventricular mass and LA size were independently associated with an increased risk of morbidity and mortality. The presence of structural remodeling and diastolic dysfunction may be useful additions to diagnostic criteria and provide important prognostic insights in patients with HFPEF.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT00095238.

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Key Words: heart failure ■ echocardiography ■ ventricular ejection fraction

Patients with heart failure and a reduced ejection fraction exhibit progressive left ventricular (LV) dilation, eccentric remodeling, and systolic dysfunction.[1,2] These pathophysiological changes in cardiac structure and function have been closely associated with increased morbidity and mortality.[1,2] Treatments that result in the reversal of these structural and functional changes also result in reduced morbidity and mortality in patients with heart failure and a reduced ejection fraction.[1,2] By contrast, the pathophysiology underlying the development of heart failure with a preserved ejection fraction (HFPEF) remains incompletely defined.[3,4] A comprehensive examination of cardiac structure and function and its association with morbidity and mortality is an important and necessary step toward meeting deficiencies in the areas of diagnosis, prognosis, and treatment in patients with HFPEF.

Clinical Perspective on p 2501

The diagnosis of HFPEF is largely made by exclusion of patients with increased LV volume and reduced ejection fraction.[4,5] Diagnostic criteria may be improved by the addition of inclusion criteria that also reflect assessment of cardiac structure and function. In addition, defining the

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relationships between structural remodeling, changes in function, and clinical outcomes may provide prognostic information. With these data, studies could be developed to test the hypothesis that the reversal of the changes in LV structure and function would result in reduced morbidity and mortality in patients with HFPEF.

We conducted a large echocardiographic substudy in patients with HFPEF as part of the Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) trial. The purpose of this echocardiographic substudy was to examine the type and prevalence of changes in cardiac structure and function present in patients with HFPEF and to determine whether these changes in structure and function are associated with alterations in morbidity and mortality.

Methods

Study Design

The I-PRESERVE trial enrolled 4128 patients; the geographic distribution of enrolled patients was presented in a previous publication[6]; 745 of these patients were also enrolled in an echocardiographic substudy in which each patient underwent 2-dimensional echocardiography and Doppler and tissue Doppler studies before randomization. To be enrolled in the echocardiographic substudy, patients had to fulfill all inclusion and exclusion criteria for the I-PRESERVE trial.[6,7] Inclusion criteria included age ≥60 years, left ventricular ejection fraction ≥45%, and recent hospitalization for heart failure or moderate to severe symptoms and corroborative objective evidence of heart failure or a cardiac substrate for diastolic dysfunction that could include any one of the following: chest x-ray, evidence of pulmonary congestion, a LBBB on ECG, echocardiographic evidence of increased wall thickness, or increased left atrial (LA) diameter. For the current echocardiographic substudy, patients had to be in normal sinus rhythm and have an echocardiographic study of adequate quality. Patients with a previous history of atrial fibrillation were not excluded as long as they were in normal sinus rhythm at time of enrollment. Table 1 provides data on the number of patients who had a previous history of atrial fibrillation.

The primary outcome for I-PRESERVE was death from any cause or hospitalization for a protocol-specified cardiovascular cause: hospitalization for worsening heart failure, myocardial infarction, stroke, unstable angina, or ventricular or atrial dysrhythmia.[7] One secondary outcome was a composite heart failure outcome consisting of death due to heart failure or hospitalization due to worsening heart failure. Deaths and hospitalizations were adjudicated by members of an independent end-point committee whose members were unaware of study-group assignments and used prespecified criteria.[8]

Echocardiographic Study

Echocardiograms were performed using a standardized protocol and standard methods of acquisition as described by the American Association of Echocardiography.[9–11] Left ventricular mass was calculated using the Devereux method, and LV volume was calculated using the area of discs method.[9–11] All echocardiograms were analyzed at the echocardiography core laboratory at the University of Maryland directed by John Gottdiener, MD.

Structure

The presence of LV dilation was determined using a partition value of LV end-diastolic volume >90 mL/m^2.[12] The presence of LV hypertrophy (LVH) was determined using partition values of LV mass indexed to height$^{2.7}$ ≥49.2 g/m$^{2.7}$ for men and ≥46.7 g/m$^{2.7}$ for women.[10] In addition, as a secondary analysis, the presence of LVH was determined using partition values of LV mass indexed to body surface area ≥115 g/m^2 for men and ≥95 g/m^2 for women.[10] In patients without LVH, concentric remodeling was defined as relative wall thickness ≥0.42 and/or LV mass/end-diastolic volume ratio (M/V) ≥1.75.[10] Left atrial size was categorized as mildly enlarged if LA area was 20 to 30 cm^2 and moderately-to-severely enlarged if LA area was >31 cm^2.[10]

Systolic Properties

Stroke work was used as an index of LV systolic performance.[13,14] Indices of LV systolic function included LV fractional shortening, ejection fraction, stroke volume, cardiac output, preload recruitable stroke work, and systolic myocardial long-axis shortening velocity (S′).[13,14] Single-beat end-systolic elastance was used as an index of LV contractility; effective arterial elastance was calculated as end-systolic pressure/stroke volume.[13,14]

Diastolic Properties

Isovolumic relaxation time was used as an index of isovolumic pressure decline. Diastolic filling was assessed using transmitral flow velocities (E, A); myocardial long-axis lengthening velocity was assessed (E′). Pulmonary capillary wedge pressure (PCWP) was estimated using the equation: PCWP=1.3[E/E′]+2 and was used to reflect ambient or instantaneous diastolic pressure; LA area was used to reflect chronic changes in diastolic pressure. The grade of diastolic dysfunction was determined using a previously published method.[15] Right ventricular systolic pressure (RVSP, mm Hg) was estimated using Doppler tricuspid regurgitant velocity (V) as RVSP=4(V^2)+10 mm Hg.

Statistical Analyses

All data are presented as mean±SD. Comparisons of baseline characteristics for patients in the echocardiographic cohort versus the remaining study cohort were examined using 2-sided Student *t* tests, Wilcoxon rank sum tests, or Fisher exact tests determined by variable type and distributional shape. To correct for the large number of comparisons made, statistically significant difference was defined as one in which the *P* value was <0.001. This conservative approach was equivalent to a Bonferroni correction for 50 comparisons. The prevalence of abnormalities in cardiac structure and function was estimated as the proportion of occurrence of each characteristic out of the substudy cohort. Normal ranges and partition values for limits of normal were obtained from echocardiographic core labs and the American Society of Echocardiography.[9,10,12,14,16] Univariate and multivariable Cox proportional hazards analyses were conducted to examine associations between outcome and continuous echocardiographic measures and to compare the clinical event rates in patients with or without specific echocardiographic characteristics. The assumptions of proportional hazards and linearity of the hazard ratios for continuous variables were assessed and found to be sufficiently met for each Cox proportional hazard model. Included in the multivariable Cox proportional hazards analysis were 7 clinical covariates (log N-terminal pro-B–type natriuretic peptide, age, diabetes mellitus, hospitalization for heart failure within 6 months preceding randomization, chronic lung disease, neutrophils, and ejection fraction) determined to be predictive of the primary and heart failure outcomes from the I-PRESERVE trial. The Kaplan-Meier cumulative event rate and survival curves were not covariate adjusted.

The overall trial and the echocardiographic substudy were approved by the ethics committee at each participating center and patients provided written informed consent. The Executive Committee, study sponsors, Steering Committee, Statistical Data Analysis Center were previously described.[6,7] This manuscript was prepared and submitted for publication by the Executive Committee, and echocardiographic core laboratory director all of whom had unrestricted access to the study data and vouch for the accuracy and completeness of the reported analyses.

Results

Demographic Characterization

The echocardiographic substudy participants represented 18% of the total I-PRESERVE enrollment. There were no clinically relevant differences between the echocardiographic

Table 1. Baseline Characteristics of Patients in the Echo Substudy vs Remaining Study Cohort

	Echo Cohort (n=745)	Study Cohort (n=3383)	*P*
Demographic characteristics			
Age			
Mean±SD, y	72±7	72±7	0.450
≥75 y, n (%)	265 (36)	1148 (34)	0.394
Female sex, n (%)	459 (62)	2032 (60)	0.457
Race, n (%)			0.005
White	713 (96)	3146 (93)	
Black	12 (2)	70 (2)	
Asian	0 (0)	34 (1)	
Other	20 (3)	132 (4)	
Clinical characteristics			
NYHA class, n (%)			0.790
II	164 (22)	706 (21)	
III	560 (75)	2584 (76)	
IV	21 (3)	91 (3)	
Heart rate, mean±SD, bpm	70±10	72±10	<0.001
Blood pressure, mean±SD, mm Hg			
Systolic	136±15	136±15	0.994
Diastolic	79±9	79±9	0.960
Body–mass index	30±5	30±5	0.418
Electrocardiographic findings, n (%)			
Left ventricular hypertrophy	210 (28)	1050 (31)	0.135
Left bundle-branch block	48 (6)	288 (9)	0.064
Ejection fraction, mean±SD, %	0.60±0.09	0.59±0.09	0.019
Cause of heart failure, n (%)			
Ischemia	150 (20)	886 (26)	0.007
Hypertension	529 (71)	2093 (62)	0.030
HF Hospitalization within previous 6 mo, n (%)	308 (41)	1508 (45)	0.112
Medical history, n (%)			
Hypertension	683 (92)	2967 (88)	0.002
Angina symptoms	277 (37)	1375 (41)	0.083
Unstable angina	58 (8)	257 (8)	0.879
Myocardial infarction	148 (20)	821 (24)	0.010
PCI or CABG	98 (13)	450 (13)	0.952
Artial fibrillation	192 (26)	1017 (30)	0.021
Diabetes mellitus	187 (25)	947 (27)	0.113
Stroke or transient ischemic attack	77 (12)	322 (11)	0.494
Quality of life			
Score on the Minnesota Living with Heart Failure scale			
Median	40	43	0.001
Interquartile range	27–54	28–59	
Laboratory measurements			
Hemoglobin			
Mean±SD, g/dL	14±2	14±2	0.640
Anemia, n (%)	76 (11)	438 (13)	0.049
Creatinine, mean±SD, mg/dL	0.99±0.31	1±0.34	0.497

(*Continued*)

Table 1. Continued

	Echo Cohort (n=745)	Study Cohort (n=3383)	P
Estimated glomerular filtration rate			
Mean±SD, mL · min^{-1} · 1.73 m^{-2} of BSA	72.3±21.6	72.6±22.7	0.738
<60 mL · min^{-1} · 1.73 m^{-2}, n (%)	222 (31)	1023 (31)	0.929
Potassium, mmol/L	4.4±0.4	4.5±0.5	0.060
NT-proBNP, pg/mL			
Median	298	352	0.058
Interquartile range	129–915	136–976	
Medications, n (%)			
Diuretic	598 (83)	2725 (83)	0.783
Loop	361 (60)	1718 (63)	0.233
Thiazide	306 (51)	1224 (45)	0.014
Spironolactone	120 (20)	501 (18)	0.395
ACE inhibitor	221 (37)	785 (29)	<0.001
Digoxin	62 (10)	482 (18)	<0.001
β-blocker	455 (76)	1905 (70)	0.017
Antiarrhythmic drug	57 (9)	294 (11)	0.384
Calcium-channel blocker	318 (53)	1271 (47)	0.010
Nitrate	169 (28)	904 (33)	0.020
Oral anticoagulant	114 (19)	650 (24)	0.012
Antiplatelet	423 (70)	1925 (71)	0.933
Lipid-lowering agent	214 (36)	1017 (37)	0.476

NT-proBNP indicates N-terminal pro brain natiuretic peptide; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; BSA, body surface area; and ACE, angiotensin-converting enzyme.

substudy patients and the remaining I-PRESERVE study cohort (Table 1).

Structure

The mean values of LV end diastolic dimension and volume were within the normal range (Table 2). Approximately 3.5% of the patients exceeded the upper limit partition value for LV end diastolic volume of 90 mL/m^2.

The mean values of LV mass and the mass/volume ratio were increased above the normal range (Table 2). Using partition values of LV mass indexed to height$^{2.7}$, LVH was present in 29% and concentric remodeling was present in an additional 25% by relative wall thickness or 30% by M/V (Figure 1). Using partition values of LV mass indexed to BSA, LVH was present in 20% and concentric remodeling was present in an additional 29% by relative wall thickness or 35% by M/V. Therefore, 54% to 59% had LVH or LV concentric remodeling.

Left atrial area was increased in 66% of the patients. Of those, the LA enlargement was mild in 51% and moderate to severe in 15% (Figure 1).

Function

The mean values for all of the indices of LV systolic chamber properties were within the normal range (Table 2). A minority had values less than the lower limit for example, EF was <50% in 7%. Using a partition value of <6.0 cm/s, S′ was abnormal in 14%.

End-systolic elastance normalized by the M/V ratio was 1.98±0.99 mm Hg/g and was within the normal range of 1.2 to 2.0 mm Hg/g. In addition, the Ees/Ea ratio was within the normal range.

Taken together, indices of LV diastolic chamber properties indicated that 31% of the patients were normal, 29% had mild grade 1 diastolic dysfunction (impaired relaxation), 36% had moderate grade 2 diastolic dysfunction (pseudonormal), and 4% had severe grade 3 diastolic dysfunction (restrictive pattern; Table 2, Figure 1).

Relationship Between Cardiac Structure and Function and Primary Study End Point

The primary end point occurred in the echocardiographic substudy at a rate comparable to the occurrence of the primary end point in the I-PRESERVE study cohort as a whole.[7] In the overall I-PRESERVE study cohort. There were 103 primary end points per 1000 patient-years, and the primary end point occurred in 36% of the randomized patients. In the echocardiographic substudy, there were 96 primary end points per 1000 patient-years and the primary end point occurred in 32%.

There was a significant association between LV mass, LV geometry, LA area, diastolic dysfunction (specifically grade 3), RVSP, and the occurrence of the primary end point in the univariate analysis. In the multivariable analysis, there was a significant association between continuous LV mass, categorical LVH, continuous LV Mass/Volume, categorical LA enlargement, and the occurrence of the primary end point (Table 3). For example, for a 10 U (g/m^2) increase in LV mass/ht$^{2.7}$ there was a 19% increase in the rate of an occurrence of the primary event (P<0.001). There was no

Table 2. Echocardiographic Data

	Echo Cohort	Normal Range
LV structure		
End-diastolic dimension, cm	4.8±0.6	4.0–6.0
End-diastolic volume, mL, mL/m^2	94±28, 49±14	80–180, 40–90
End-systolic dimension, cm	3.2±0.7	2.0–4.0
End-systolic volume, mL, mL/m^2	35±19, 18±9	25–50, 15–25
Wall thickness, cm	0.93±0.15	0.8–0.9
Mass, g, g/ht$^{2.7}$	164±48, 43±12	80–140, 18–38
Relative wall thickness	0.40±0.08	0.36–0.40
Mass/EDV, g/mL	1.95±0.80	1.25–1.75
LV systolic properties		
Fractional shortening, %	43±10	30–45
Ejection fraction, %	64±9	55–75
Stroke volume, mL	59±24	50–70
Cardiac output, L/min	3.9±1.6	3.5–5.0
S′, lateral, cm/sec	8.2±2.3	6–14
Stroke work, kg · cm	6.7±3.0	5–10
Preload recruitable stroke work, kg/cm^2	90±27	75–125
Ees, mm Hg/mL	3.6±2.0	1.2–3.0
Ea, mm Hg/mL	1.9±0.8	1.2–1.8
LV diastolic properties		
E, cm/sec	78±28	40–90
A, cm/sec	83±26	40–100
E/A	1.05±0.74	0.6–1.4
E′ lateral annulus, cm/sec	9.1±3.4	7.0–11.5
E′ septal annulus, cm/sec	7.2±2.9	5.0–11.0
E/E′ lateral	10.0±4.5	4.5–11.5
PCWP, mm Hg	15±6	5–12
IVRT, ms	95±22	60–130
E deceleration time, ms	216±77	185–310
Left atrial area, cm^2, cm^2/m^2	23±6, 12±3	10–20, 5–10
RV systolic pressure	37±13	15–25

Values are mean±SD unless otherwise indicated. Normal Range is adjusted for the average age of the echo cohort (70 years).

EDV indicates end-diastolic volume; DT, mitral valve deceleration time; IVRT, isovolumic relaxation time; E, peak early diastolic filling velocity; A, peak late diastolic filling velocity during atrial contraction; E′, mitral lateral and septal annular tissue velocity during early filling; S′, mitral lateral annular tissue velocity during systole; Ees, end-systolic elastance; Ea, arterial elastance; PCWP, pulmonary capillary wedge pressure; and RV, right ventricle.

relationship with categorical diastolic dysfunction (grade 1–3). There were no significant associations between E, E/A, E′, E/E′, IVRT, or DT and the occurrence of the primary end point or the heart failure end point examined in the multivariate analysis. Complete data are presented in the online-only Data Supplement. The Kaplan-Meier curves shown in Figure 2 demonstrate that the cumulative event rate was higher in patients with LVH, LA enlargement, or grade 3 diastolic dysfunction. Kaplan-Meier curves plotting survival are presented in the online-only Data Supplement.

Relationship Between Cardiac Structure and Function and Heart Failure End Point

The heart failure end point occurred in the echocardiographic substudy at a rate comparable to the occurrence of the heart failure end point in the I-PRESERVE study cohort as a whole.[7] In the I-PRESERVE study cohort, there were 47 heart failure end points per 1000 patient-years and the heart failure end point occurred in 17% of the randomized patients. In the echocardiographic substudy, there were 41 heart failure end points per 1000 patient-years and the heart failure end point occurred in 14%.

There were significant associations among LV mass, LV geometry, LA area, diastolic dysfunction (specifically grade 3), RVSP, and the occurrence of the heart failure end point in the univariate analysis. In the multivariable analysis, there was a significant association between continuous LV mass, categorical LVH, continuous M/V ratio, continuous LA area, and categorical LA enlargement and the occurrence of the heart failure end point (Table 3). For example, for a 1-U (cm^2) increase in LA area, there was a 3.6% increase in the rate of a heart failure event ($P<0.05$). There was a 226% increase in the risk of a heart failure event for those who had LA enlargement compared with those who did not ($P<0.05$). The Kaplan-Meier curves shown in Figure 2 demonstrate that the cumulative event rate for the heart failure outcome was increased in patients with LVH, LA enlargement, or Grade 3 diastolic dysfunction. Kaplan-Meier curves plotting survival are presented in the online-only Data Supplement.

Discussion

There were 2 principal findings of the I-PRESERVE echocardiographic substudy. First, our patients with HFPEF had a high prevalence of structural remodeling characterized by significant concentric LV remodeling and LVH and a high prevalence of diastolic dysfunction as evidenced both by abnormal echocardiographic-Doppler indices and increased LA area. Second, the presence of these changes in structure and function was independently associated with an increased risk of morbidity and mortality. This risk remained significantly elevated even after known risk factors, including N-terminal pro-B–type natriuretic peptide, were included in the multivariable analysis. These findings may be pivotal to the development of improved diagnostic criteria and prognostic assessment of patients with HFPEF. In addition, these findings may enhance our understanding of the pathophysiology underlying the clinical heart failure in these patients.

Structural Remodeling

Left ventricular structural remodeling is characterized by quantitation of LV mass, volume, and geometry. It is important to recognize that even when LVH is not present, cardiomyocyte cellular hypertrophy can still occur, LV mass can be increased compared to a patient's preexisting baseline, and LV mass can be increased relative to LV volume. It is likely that the observed substantial prevalence of concentric remodeling reflects these changes even in the absence of LVH.

Patients with HFPEF have clinical characteristics that place them at substantial risk for developing LVH and

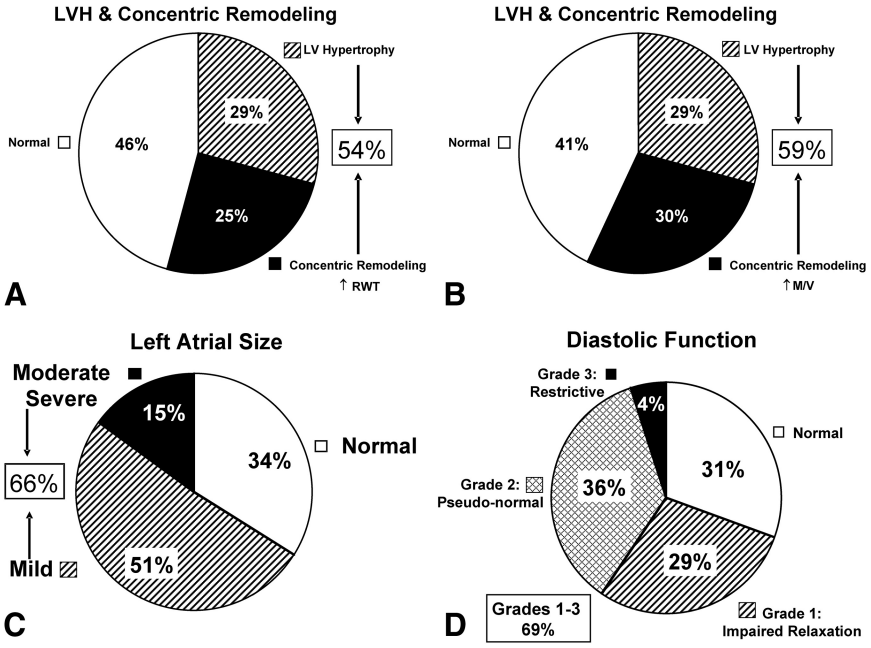

Figure 1. A, Prevalence of concentric remodeling using relative wall thickness criteria and LVH using sex-specific partition values of LV mass indexed to height.[2,7] In patients with HFPEF, the prevalence of LVH was 29% and that of concentric remodeling was 25%. **B**, Prevalence of concentric remodeling using M/V criteria and LVH. In patients with HFPEF, the prevalence of LVH was 29%, and that of concentric remodeling was 30%. Thus, the majority of HFPEF patients had LV structural remodeling. **C**, Prevalence LA enlargement. In patients with HFPEF, the prevalence of LA enlargement was 66%. Because LA size reflects LV diastolic pressure integrated over time, these data indicate that the majority of HFPEF patients had increased diastolic pressure. **D**, Prevalence of diastolic dysfunction classified by grade 1 to 3. In patients with HFPEF, the prevalence of diastolic dysfunction was 69%. Thus, the majority of HFPEF patients had diastolic dysfunction. LVH indicates left ventricular hypertrophy; LV, left ventricular; RWT, relative wall thickness; and M/V, LV mass/end-diastolic volume ratio.

concentric remodeling.[7,13–15,17–25] For example, HFPEF patients are older, more often women, have a high prevalence of hypertension, and a large number of comorbidities, each of which increase the risk for developing concentric remodeling. However, the prevalence of LVH and concentric remodeling in the current study was at least as high as would be expected on the basis of the presence of these characteristics alone. Previous smaller studies of unselected patients support this finding.[18,19]

In HFPEF patients, a variety of risk factors may contribute to the resultant morbidity and mortality rates. These include underlying disease processes such as hypertension and diabetes mellitus, age, sex, and other comorbidities. However, the heart failure morbidity in I-PRESERVE (heart failure hospitalization rate of 47/1000 patient years) was substantially higher than that observed in recent hypertension and diabetes studies (heart failure hospitalization rate of 2.5–11.5/1000 patient years).[26–33] Data from the current study, fully adjusted for other important covariates, suggests that the presence of structural remodeling, particularly LVH, in HFPEF patients is associated with and may contribute mechanistically to an increased risk of morbidity and mortality.

One consequence of using data from a randomized clinical trial to characterize changes in structure (discussed above) and function (discussed below) is the lack of a control group from which to derive normal ranges and normal limit partition values. We used normal ranges and partition values taken from echocardiographic core laboratories, consensus guidelines from the American Society of Echocardiography, and other published studies.[9,10,12,14,16] The ranges and partition values chosen were adjusted for age and sex. The analyses based on these normal ranges added important insights and provided important context for interpretation. Despite the care taken in these choices, statistical comparisons would be improved by using a simultaneously enrolled cohort with comparable age, sex, race, geographical distribution, and comorbidity profile.

Diastolic Properties

In the current echocardiographic substudy, the presence of diastolic dysfunction was assessed using indices of LV pressure decline, filling, and distensibility. These indices were used in combination to determine the grade or severity of diastolic dysfunction and to estimate ambient LV diastolic filling pressure.[15] In addition, changes in LA size were used to evaluate LV diastolic pressure and integrate changes in LV diastolic pressure over time. That is, even when ambient LV diastolic pressures are normal, an increased LA size reflects the length and severity of the increased LV diastolic pressure over time.

The same demographic and clinical characteristics that place patients with HFPEF at high risk of developing structural remodeling also increase the likelihood of developing diastolic dysfunction. However, the prevalence of diastolic dysfunction in the current study was higher than would be expected on the basis of the presence of these clinical characteristics alone.[15,20,30] For example, in cross-sectional population studies of patients with age >65 years, diastolic dysfunction was present in 15% to 30%.[11] In older patients with hypertension, coronary artery disease, and/or diabetes mellitus, the prevalence of diastolic dysfunction was 50% to 60%.[26–33] The highest prevalence however is in patients with symptomatic heart failure, particularly patients with HFPEF.

Data from the current study are concordant with previous HFPEF studies, which have shown that the prevalence of diastolic dysfunction approaches 70%.[17–25] In these previous studies, morbidity and mortality events were higher in patients with diastolic dysfunction as measured by echocardiographic parameters or LA size. However, in the current study, echocardiographic and Doppler indices of diastolic dysfunction did not have significant prognostic value and were not associated with an increase in cardiovascular events. By contrast, LA enlargement did have significant prognostic value. The apparent discrepancy between prognostic value of

Table 3. Association Between Baseline Cardiac Structure and Function and Clinical Outcomes

	Univariate Analysis			Multivariable Analysis*	
Primary End Point Variable	Event Rate, per 1000 Patient y	HR (95% CI)	*P*	HR (95% CI)	*P*
LV mass/HT$^{2.7}$					
Per 1-unit increase		1.028 (1.019–1.037)	<0.001	1.019 (1.009–1.029)	<0.001
LV hypertrophy					
No	76.1	Reference		Reference	
Yes	143.0	1.860 (1.404–2.464)	<0.001	1.589 (1.168–2.161)	0.003
LV mass/volume ratio					
Per 1-unit increase		1.265 (1.070–1.496)	0.006	1.296 (1.074–1.564)	0.007
High mass-to-volume ratio					
No	84.3	Reference		Reference	
Yes	104.8	1.241 (0.918–1.677)	0.160	1.303 (0.940–1.807)	0.112
LA area					
Per 1-unit increase		1.042 (1.024–1.061)	<0.001	1.013 (0.992, 1.034)	0.235
Enlarged LA Area					
No	59.8	Reference		Reference	
Yes	119.2	1.983 (1.445–2.722)	<0.001	1.470 (1.029, 2.101)	0.034
Diastolic dysfunction					
Grade 0	75.8	Reference		Reference	
Grade 1	64.3	0.851 (0.522–1.388)	0.518	0.673 (0.402–1.128)	0.133
Grade 2	95.7	1.261 (0.823–1.933)	0.287	1.027 (0.660–1.600)	0.905
Grade 3	205.1	2.662 (1.355–5.231)	0.005	1.461 (0.726–2.941)	0.288
Heart failure end point					
LV mass/HT$^{2.7}$					
Per 1-unit increase		1.031 (1.018–1.044)	<0.001	1.025 (1.011–1.039)	<0.001
LV hypertrophy					
No	32.4	Reference		Reference	
Yes	70.2	2.145 (1.434–3.209)	<0.001	1.901 (1.223–2.955)	0.004
LV mass/volume ratio					
per 10unit increase		1.412 (1.121–1.779)	0.004	1.487 (1.141–1.937)	0.003
High mass-to-volume ratio					
No	34.9	Reference		Reference	
Yes	44.6	1.275 (0.810–2.006)	0.295	1.431 (0.871–2.351)	0.157
LA area					
Per 1-unit increase		1.066 (1.041–1.092)	<0.001	1.036 (1.008–1.065)	0.011
Enlarged LA area					
No	16.3	Reference		Reference	
Yes	56.7	3.521 (2.003–6.189)	<0.001	2.264 (1.243–4.124)	0.008
Diastolic dysfunction					
Grade 0	27.9	Reference		Reference	
Grade 1	23.5	0.851 (0.386–1.874)	0.688	0.775 (0.340–1.673)	0.488
Grade 2	42.7	1.567 (0.810–3.029)	0.182	1.227 (0.621–2.422)	0.556
Grade 3	83.9	3.095 (1.115–8.596)	0.030	1.500 (0.527–4.268)	0.447

*Covariates in the adjusted model included: Log NT-proBNP, age, diabetes mellitus, hospitalization for worsening heart failure within 6 months preceding randomization, COPD or asthma, neutrophils, and ejection fraction.

LV indicates left ventricular; BSA, body surface area; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval; LA, left atrial; and HT, height.

LA size and Doppler indices and the differences with previous studies may have a number of explanations. Changes in LA size result from both the extent and duration of increased LV diastolic pressure (ie, the integrated area under the pressure-versus-time relationship). By contrast, Doppler and tissue Doppler indices such as E, E′, and the E/E′ ratio represent LV diastolic pressures at 1 point in time and are very sensitive to changes in LV load. Because all of the

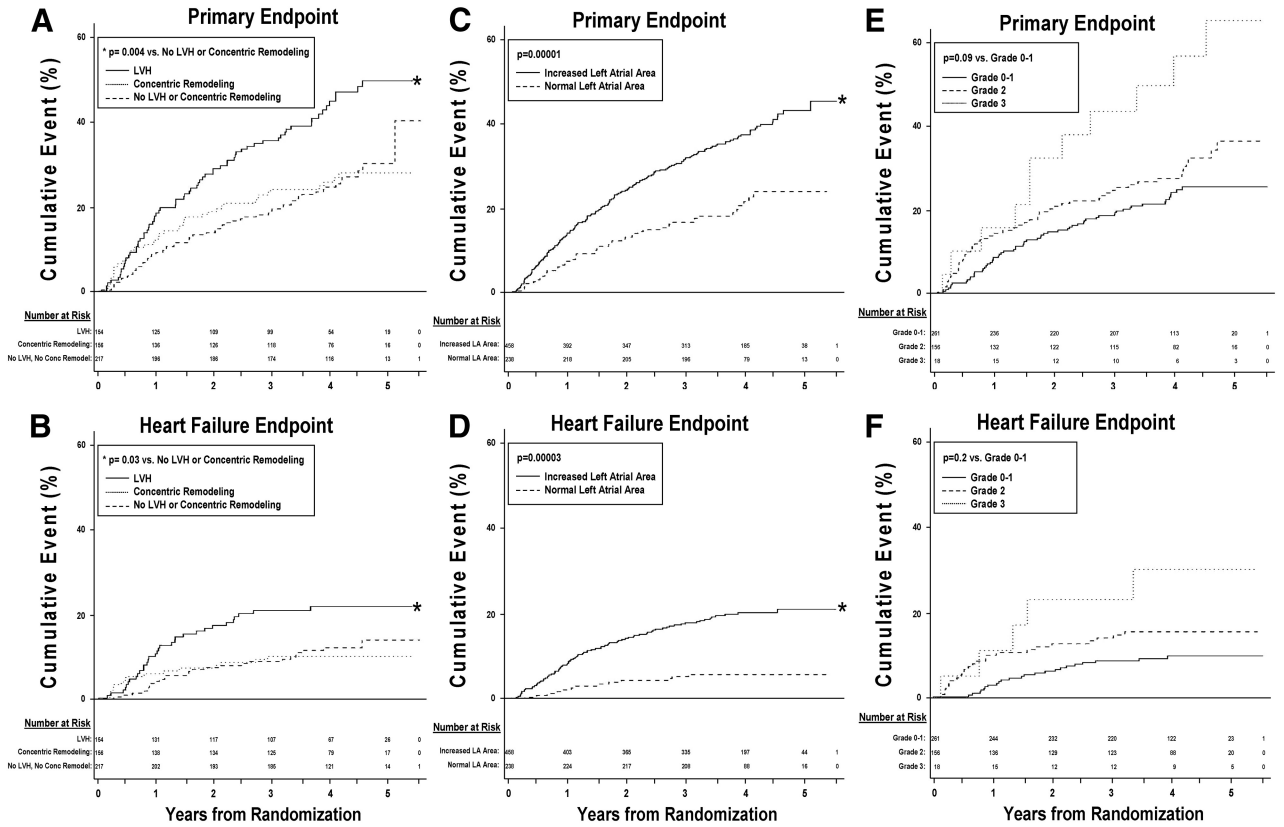

Figure 2. The presence of LVH was associated with an increased cumulative event rate of the primary study end point (**A**) and the heart failure end point (**B**) in patients with HFPEF. The presence of an increased LA area was associated with increased cumulative event rate of the primary study end point (**C**) and the heart failure end (**D**) in patients with HFPEF. The presence of diastolic dysfunction grade 3 increased cumulative event rate of the primary study end point (**E**) and the heart failure end point (**F**) in patients with HFPEF. LVH indicates left ventricular hypertrophy; LA, left atrial.

patients enrolled in I-PRESERVE were very well compensated, ambient LV diastolic pressures at the time of the baseline echocardiogram were expected to be only mildly increased. On the other hand, these patients were expected to have a long history of variably increased LV diastolic pressures, especially during exercise, activity, and periods of decompensation. These increases, over the long term, would be reflected in increased LA size. Therefore, it seems reasonable that the best diastolic function prognostic index was LA size.

Systolic Properties

Overall, the average values of all of the indices used to reflect LV systolic properties for the HFPEF patients studied in the I-PRESERVE echocardiographic substudy fell within the normal ranges presented in Table 2. These results were concordant with previous studies of patients with HFPEF.[13,14,18,19] However, these data should not be interpreted to indicate that there are no abnormalities in any single systolic index in any individual patient with HFPEF. For example, the velocity of long-axis shortening (S′) fell below the lower limit partition value in 14% of the HFPEF patients in our study. A small percentage of our patients also had decreased values of other systolic properties, including 7% of the patients with an ejection fraction <50%. In addition, no measurements of systolic parameters were made during exercise or stress. It has been suggested that abnormalities in arterial stiffness and ventricular-vascular coupling may be abnormal in HFPEF. In the current study, whereas indices of systolic stiffness (Ees) and arterial stiffness (Ea) were both increased, the ratio Ees/Ea, an index of ventricular-vascular coupling, fell within the normal range in our patients with HFPEF.

Relationship Between Structure/Function and Morbidity/Mortality

The I-PRESERVE echo substudy is the largest randomized clinical trial to be able to provide prognostic information in patients with HFPEF that relates morbidity and mortality to cardiac structure and diastolic function. Recently, Komajda et al used 58 demographic, clinical, and biological variables in a multivariable Cox proportional hazard regression model to examine morbidity and mortality in the HFPEF patients studied in I-PRESERVE.[34] Seven clinical variables, Log NT-proBNP, age, diabetes mellitus, hospitalization for heart failure within 6 months preceding randomization, chronic lung disease, log neutrophil count, and ejection fraction, were the strongest multivariable predictors of morbidity and mortality outcomes. In the current echo substudy, these 7 clinical variables were added to the multivariable model used to examine the predictive value of echocardiogram-derived structural and functional characteristics. Left ventricular mass, LVH, LA area, LA enlargement, and the mass/volume ratio, independent of these 7 clinical variables, were found to

be predictive of morbidity and mortality in HFPEF patients. Therefore, using clinical variables plus echo variables of structure and diastolic function should enable identification of a population of HFPEF patients who are at increased risk of developing mortal and morbid events. The utility of diastolic function grade was limited in the current study. This may reflect the limitation that some patients could not be placed in a specific grade, were indeterminate, and reduced the sample size for analysis.

Within different studies, there are significant differences in the prevalence of structural remodeling and abnormalities in function and their relationship to clinical outcomes in patients with HFPEF that appear to be based on the specific populations examined. Each population studied has some advantages and some disadvantages. Taken together, the aggregate data allow characterization of patients with HFPEF and some limited insights into underlying pathophysiology. However, pathophysiological mechanisms, beyond those examined in and shown to have importance in the current analysis, may play a role in HFPEF patients. For example, the prevalence of structural remodeling and abnormalities in function in HFPEF patients enrolled from populations at the time of hospitalization for acute decompensated heart failure will differ from those of patients enrolled as outpatients with compensated heart failure. Prevalence will differ depending on the specific nature of the inclusion and exclusion criteria, the geographic location, age, sex, and racial mix of the enrolled population. Several studies illustrate these points.[14,15,17–25,35–37]

Klapholz et al examined 619 patients from the New York Heart Failure Consortium that were hospitalized with acute decompensated heart failure.[35] Some of the patients enrolled had valvular heart disease, >15% had severe valvular heart disease, and >75% had some valvular heart disease. Klapholz reported 5 echocardiographic measurements: LV ejection fraction, LV mass, right ventricular systolic pressure, and LV end-diastolic and end-systolic dimension. In this study, 82% of the patients had LVH. These structural and functional measurements were not examined with respect to clinical outcome. By contrast, I-PRESERVE examined patients who had compensated HFPEF and who were outpatients at the time of enrollment. Valvular heart disease was excluded from I-PRESERVE; 28 parameters of structure and function were examined, and 4 of these were associated with clinical outcome.

Four publications from the Olmsted County Study reported aspects of the structural and functional changes in 244 patients with HFPEF.[15,18,36,37] This epidemiological cohort found similar structural abnormalities in their HFPEF patients and also related pulmonary artery systolic pressure, LV midwall fractional shortening, and ejection fraction to survival. Although the demographics of the Olmsted County patients were similar to those of the current study, there were important differences in Methods that serve to extend the findings in the Olmsted studies. I-PRESERVE examined >3 times the sample size of the Olmsted County studies and related structural and functional parameters to mortality, morbidity, and a comprehensive heart failure end point, and all end points were adjudicated by a blinded end-points committee using standardized definitions of these mortality and morbidity end points.

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Echocardiographic Substudy (CHARMES) is the only other randomized clinical trial involving patients with HFPEF studied echocardiographically.[17] There is good concordance in prevalence of structural and functional findings between the 312 subjects in CHARMES and the 745 subjects enrolled in I-Preserve. Persson et al found a similar prevalence of LVH, LA enlargement, and diastolic dysfunction compared to the current study. Person et al also found a significant association between diastolic dysfunction and outcome (increased hazard of death/heart failure hospitalization). There are however, significant differences in the demographic characteristics in CHARM versus I-Preserve, described in detail in McMurray et al that demonstrates that I-Preserve subjects were more concordant with epidemiological studies of patients with HFPEF.[38] The echocardiograms in CHARMES were performed 14 months after randomization. In addition, CHARMES only examined the relationship of diastolic dysfunction to outcome whereas I-PRESERVE also examined relationships between LV mass, geometry and LA size.

Potential Application of Measurements of Cardiac Structure and Function in HFPEF Diagnosis and Management

Heart failure is a clinical syndrome; therefore, the diagnosis of heart failure is based on clinical symptoms and signs that indicate increased diastolic filling pressures, decreased cardiac output, or both. However, symptoms and signs of heart failure lack specificity and can be confused with other comorbidities such as aging, obesity, deconditioning, and pulmonary and venous disease. Therefore, the presence of objective evidence indicating increased diastolic filling pressures and/or decreased cardiac output have been used to support this clinical diagnosis. Among the methods used to provide this objective evidence, measurements of structural remodeling and abnormal function have proven efficacy in patients with heart failure and a reduced ejection fraction.

Similar structural and functional abnormalities have been sought for patients with HFPEF. The current study suggests that the presence of LVH, concentric remodeling, LA enlargement, and diastolic dysfunction could be used to support the diagnosis of heart failure in patients with HFPEF. Although these findings on echocardiography would not be obligatory criteria to diagnose HFPEF, the absence of any evidence of structural remodeling or abnormal diastolic function would place the diagnosis in doubt. All 745 patients in the current study had at least 1 of the following findings: LVH, concentric remodeling, LA enlargement, and diastolic dysfunction. These findings serve to support already proposed diagnostic criteria for HFPEF and should be used as inclusion criteria in future clinical studies.[1–5] In addition, the current study suggests that changes in cardiac structure and function contribute prognostic information to patients with HFPEF. Finally, the correction of abnormal LV structure and function in HFPEF may constitute reasonable therapeutic

targets to reduce morbidity and mortality in patients with HFPEF.

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Disclosures

Drs Zile, Gottdiener, and Carson report receiving consulting fees from Bristol-Myers Squibb and Sanofi-aventis. Dr McMurray reports receiving support from Bristol-Myers Squibb (to Glasgow University) for his work on this trial. Dr Komajda reports receiving consulting fees from Bristol-Myers Squibb and Servier and lecture fees from Sanofi-aventis. Dr McKelvie reports receiving consulting fees and lecture fees from Bristol-Myers Squibb and Sanofi-aventis. S.J. Hetzel reports being employed by the Statistical Data Analysis Center at the University of Wisconsin Madison, which conducted the statistical analysis for this trial that was supported by Bristol-Myers Squibb and Sanofi-Aventis. Dr Massie reports receiving grant support and consulting fees from Bristol-Myers Squibb and Sanofi-aventis.

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CLINICAL PERSPECTIVE

The purpose of this study was to examine the prevalence and pattern of structural remodeling and alterations in function present in patients with heart failure and a preserved ejection fraction (HFPEF) and to determine whether there was an association among changes in cardiac structure, function, morbidity, and mortality. An echocardiographic substudy of the Irbesartan in Heart Failure with Preserved Ejection Fraction trial (I-PRESERVE) enrolled 745 patients. Structural remodeling and diastolic dysfunction was present in the majority of patients with HFPEF. Structural remodeling and diastolic dysfunction predicted clinical outcomes. Increased left ventricular mass, mass/volume ratio, and left atrial size were independently associated with an increased risk of morbidity and mortality. These findings may be pivotal to the development of improved diagnostic criteria and prognostic assessment of patients with HFPEF. For example, the inclusion of measurements of left ventricular mass, geometry, and diastolic function could be added to the diagnostic criteria for HFPEF and could be used to predict the risk of morbidity and mortality in patients with HFPEF. With these data, studies could be developed to test the hypothesis that the reversal of the changes in left ventricular structure and function would result in reduced morbidity and mortality in patients with HFPEF. Taken together, these findings serve to enhance our understanding of the pathophysiology underlying clinical heart failure in these patients with HFPEF.

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SUPPLEMENTAL MATERIAL

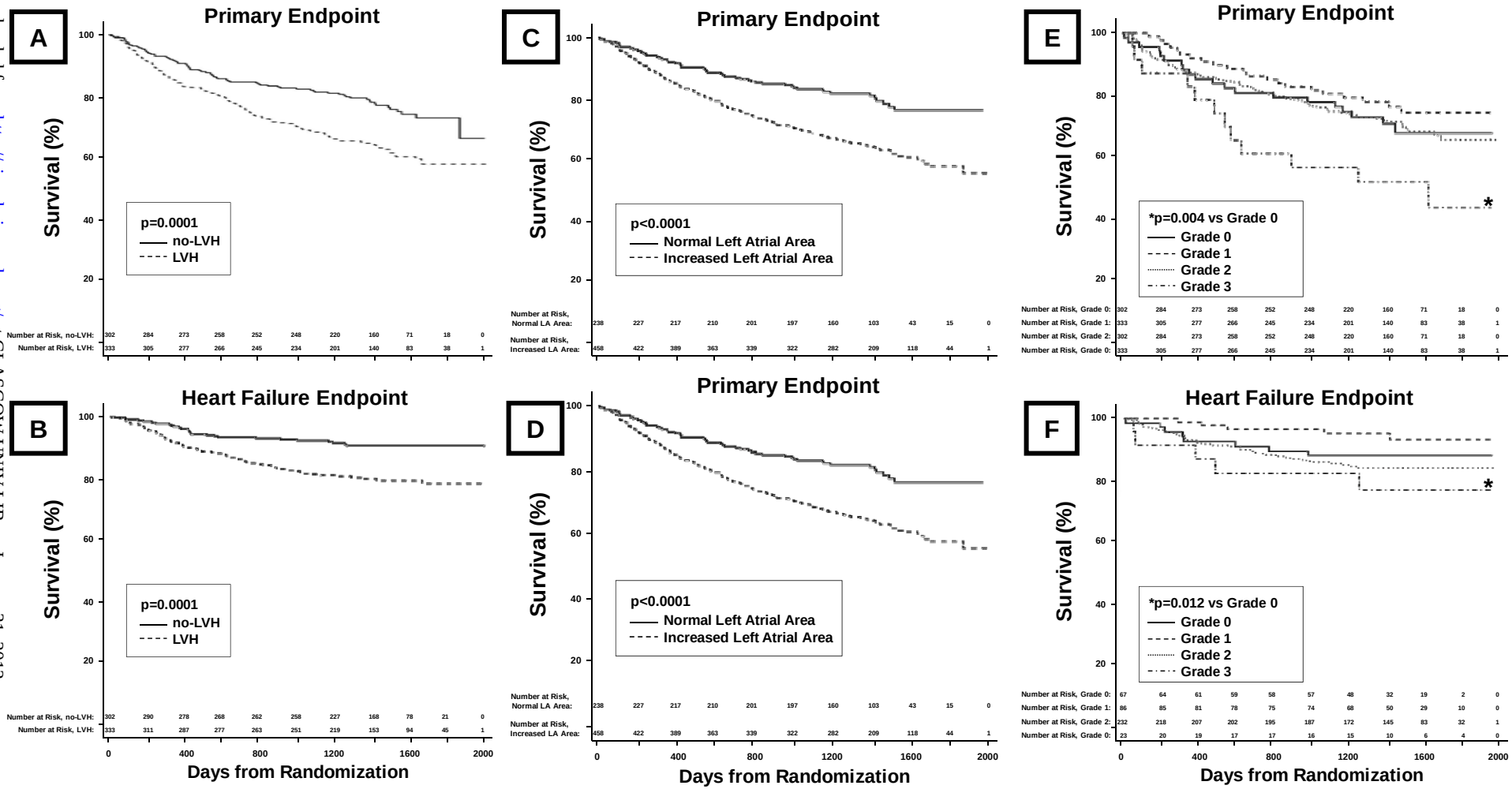

Figure Legend for Supplemental Figure:

The presence of left ventricular hypertrophy (LVH) was associated with a decreased survival rate of the primary study endpoint (Panel A) and the heart failure endpoint (Panel B) in patients with HFPEF.

The presence of an increased left atrial area was associated with a decreased survival rate of the primary study endpoint (Panel C) and the heart failure endpoint (Panel D) in patients with HFPEF.

The presence of diastolic dysfunction grade 3 decreased the survival rate of the primary study endpoint (Panel E) and the heart failure endpoint (Panel F) in patients with HFPEF.

Supplemental Table: Association Between Baseline Indices of Diastolic Function and Clinical Outcomes

Primary Endpoint

	Univariate Analysis		Multivariable Analysis [2]	
Variable	**HR (95% C.I.)**	**P-value**	**HR (95% C.I.)**	**P-value**
E	1.007 (1.003, 1.012)	< 0.001	0.999 (0.995, 1.004)	0.724
E/A	1.321 (1.170, 1.491)	< 0.001	0.992 (0.846, 1.163)	0.918
E’	1.046 (1.005, 1.090)	0.029	1.016 (0.973, 1.061)	0.468
E/E’	1.014 (0.985, 1.044)	0.349	0.981 (0.949, 1.015)	0.264
IVRT	0.998 (0.992, 1.005)	0.574	1.004 (0.998, 1.011)	0.220
DT	0.998 (0.996, 1.000)	0.028	0.999 (0.997, 1.001)	0.433

Heart Failure Endpoint

	Univariate Analysis		Multivariate Analysis	
Variable	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
E	1.013 (1.007, 1.019)	< 0.001	1.004 (0.997, 1.010)	0.275
E/A	1.421 (1.221, 1.654)	< 0.001	1.055 (0.855, 1.303)	0.615
E’	1.093 (1.035, 1.155)	0.001	1.040 (0.978, 1.107)	0.209
E/E’	1.002 (0.954, 1.052)	0.949	0.977 (0.926, 1.031)	0.394
IVRT	0.994 (0.984, 1.004)	0.252	1.002 (0.992, 1.012)	0.683
DT	0.996 (0.993, 0.999)	0.006	0.998 (0.995, 1.001)	0.208

Abbreviations: DT = mitral valve deceleration time, IVRT = isovolumic relaxation time, E = peak early diastolic filling velocity, A = peak late diastolic filling velocity during atrial contraction, E’ = mitral lateral annular tissue velocity during early filling, HR = hazard ratio, CI = confidence intervals.

[2] Covariates in the adjusted model included: Log NT-proBNP, age, Diabetes Mellitus, hospitalization for worsening heart failure within 6 months preceding randomization, COPD or asthma, neutrophils, and ejection fraction.